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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET

The amendment filed 1/5/2009 under 37 CFR 1.116 in reply to the final rejection has NOT been entered. The final Office action, mailed 12/8/2008, is maintained.

Continuation of PTOL-324, Notice of Non-Compliant Amendment

The amendment to the claims filed on 1/5/2009 does not comply with the requirements of 37 CFR 1.121(c) because the claim listing does not commence on a separate sheet of the amendment document. The sheet containing claim 1 contains other parts of the amendment document. Furthermore, claim 32 has not been provided with the proper status identifier. Claim 32 has the status identifier "withdrawn"; however, the claim is not withdrawn. The status identifier for claim 32 should be "previously presented." Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(1) *Claim listing.* All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1–5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter

must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

Continuation of PTOL-303, Advisory Action Before the Filing of an Appeal Brief

The proposed amendment to claim 38 would require further search and consideration. The proposed amendment broadens the scope of the claim by not requiring a specific cell density for the re-plating. Furthermore, the addition of new claims 39 and 40 would require further search and/or consideration, because they were not previously presented.

The proposed addition of claim 40 raises the issue of new matter. The claim requires that the "upper plate has not intended surface roughness to expose a greater surface anchoring area to cells for attachment." The as filed specification does not provide support for the presence or absence of surface roughness on the upper plate. Applicant has not cited portions of the as filed specification that provide support.

With respect to the rejection of claims 1, 4, 6, 9, 11, 32, 33 and 35-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Riser et al and Burkitt et al, Applicant's arguments filed 1/5/2009 have been fully considered but they are not persuasive.

In section 2, Applicant essentially asserts that the claimed method is not taught in full by Example 1 or Example 6 of Caplan et al. Specifically, the response notes that Example 1 does not teach the transfer of the bone marrow aspirate in medium to a culture device comprising an upper plate with pores and a lower plate base, and Example 6 only uses DMEM. The response notes that Caplan et al do not use complete medium in Example 6. It appears as though Applicant is arguing that the DMEM used in Example 6 does not meet the limitation of a culture medium "containing factors that stimulate mesenchymal stem cell growth without differentiation and allowing for the selective adherence of only the mesenchymal stem cells to substrate surface." This argument is not persuasive, because Caplan et al teach, "Several media were prepared which were particularly well suited to the desired selective attachment and are referred herein as 'complete media' when supplemented with serum as described below. One such medium is an augmented version of Dulbecco's Modified Eagle's Medium (DMEM), which is known and readily available." See column 8, lines 45-49. The rejection of record is made under 35 U.S.C. 103(a), and the single reference is not required to anticipate the claimed invention. It would have been within the ordinary skill in the art at the time the invention was made to replace the DMEM with complete medium for administration to a culture dish comprising a porous plate. As noted by Applicant, Example 1 teaches the use of DMEM or complete medium. Thus, one would have recognized that complete medium could be used in place of DMEM.

In section 3, Applicant notes that Caplan et al used the Leukosorb™ to remove fat, red blood cells and plasma from the mesenchymal stem cells. The response asserts that the Leukosorb™ filter, or its derivatives, which absorb or trap leukocytes, cannot remove leukocytes. The response cites art, which indicates that anticoagulants can cause leukocytes to pass through or be trapped by the Leukosorb™ filter. Further, the response notes that Caplan used heparin to collect the bone marrow aspirate used for isolating mesenchymal stem cells (e.g., paragraph bridging columns 45-46). Thus, the response notes that the Leukosorb™ filter will capture 100% of the leukocytes. The response asserts that the upper plate used in the present specification was used to remove small-sized cells such as leukocytes. The response asserts that it would not have been obvious to one of ordinary skill in the art to use the Leukosorb™ filter.

These arguments are not found persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., removal of leukocytes) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In section 4, the response asserts that there was not problem in the disclosure of Caplan et al, and thus one would not want to combine the teachings of Caplan et al and Rieser et al. Further, the response asserts that the obvious rejection did not present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.

These arguments are not found persuasive. The Supreme Court in KSR reaffirmed the familiar framework for determining obviousness as set forth in Graham v. John Deere Co. (383 U.S. 1, 148 USPQ 459 (1966)), but stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way. KSR, 550 U.S. at ___, 82 USPQ2d at 1391. Specifically, the Supreme Court stated that the Federal Circuit had erred in four ways: (1) "by holding that courts and patent examiners should look only to the problem the patentee was trying to solve " (Id. at ___, 82 USPQ2d at 1397); (2) by assuming "that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem" (Id.); (3) by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try'" (Id.); and (4) by overemphasizing "the risk of courts and patent examiners falling prey to hindsight bias" and as a result applying "[r]igid preventative rules that deny fact finders recourse to common sense" (Id.). Thus, Caplan et al need not disclose a problem that must be solved by Rieser et al. Caplan et al teach that unwanted cells, such as red blood cells and fat cells, can be removed from a population of cells comprising mesenchymal stem cells by passing the smaller red blood cells and fat cells through a filter. Rieser et al teach a culture dish comprising a porous plate. At the time the invention was made, one would have recognized that small, unwanted cells such as red blood cells would pass through the holes in the plate. Thus, the plate of Rieser et al would serve the same function as the filter of Caplan et al, and one would not have to perform the extra steps of washing the cells from the filter or perform additional purification steps as taught by Caplan et al.

In section 5, the response notes that Rieser et al discredit the use of the filter material in US Patent NO. 5,326,357 (column 2, lines 42-46). Thus, the response asserts it would be illogical that one with ordinary skill in the art read Rieser's teachings and then used the element function as a filter as they disbelieved. This argument is not found persuasive, because the teachings of US Patent No. 5,326,357 are not relied upon in the instant rejection. The rejection is not based upon the use of the filter material of US Patent No. 5,326,357. Rieser et al state that the method described in US Patent No. 5,326,357 involved applying chondrocytes to a filter material (MILLICELL®-CM). The combined teachings of Caplan et al and Rieser et al are not directed to the application of chondrocytes to a MILLICELL®-CM filter.

In section 6, the response asserts that the isolating efficiency of the method of Rieser et al is "far behind from this application because that the surface roughness of bone substitute exposes a greater surface anchoring area to cells for attachment." This argument is not found persuasive, because the claims do not require a particular isolating efficiency. The claims encompass any isolating efficiency. Further, the response asserts that Rieser et al teach hydroxyapatite for the surface upon which the mesenchymal stem cells are cultured and this surface will induce osteogenic differentiation. Thus, the response asserts that the culture conditions will not maintain the mesenchymal stem cells as undifferentiated cells for isolating. These arguments are not found persuasive. Claim 1 requires the following steps: "(a) providing a cell mixture comprising mesenchymal stem cells and other cells in a culture medium, said the culture medium containing factors that stimulate mesenchymal stem cell growth without differentiation and allowing for the selective adherence of only the mesenchymal stem cells to substrate surface; (b) seeding and culturing the cell mixture in a culture device comprising an upper plate with

pores and a lower plate base, said the upper plate made of the mesenchymal stem cell adhering material, where mesenchymal stem cells are adhered and cultured, and the lower plate base, where the other small-sized cells adhered following passing through the pores in the upper plate; and (c) removing non-adherent cells on the upper plate by changing medium." In step (a), the claim defines the culturing medium using functional language, which is "containing factors that stimulate mesenchymal stem cell growth without differentiation and allowing for the selective adherence of only the mesenchymal stem cells to substrate surface." The claims do not relate back to the "substrate surface" of step (a). Caplan et al teach a medium that meets the claim limitations. Specifically, Caplan et al teach that complete medium contains factors that stimulate mesenchymal stem cell growth without differentiation and allows for the selective attachment through specific protein binding sites of only mesenchymal stem cells to plastic surfaces (e.g., column 9, lines 45-55). Further, the claim does not require the mesenchymal stem cells to be cultured without differentiation. The ability of the cells to differentiate into ostoeblasts and form bone is consistent with claim 9, which requires the mesenchymal stem cells to be capable of differentiating into tissues comprising bone.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Applicant's arguments, see section 6, filed 1/5/2009, with respect to the rejection of claims 35-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Rieser et al and Burkitt et al have been fully considered and are persuasive. The previous rejection of claims 35-38 has been withdrawn. Caplan et al teach that mesenchymal stem cells cultured for 14-21 days become confluent. Applicant has provided evidence that cells cultured for 14 days

on a hydroxyapatite support differentiate to osteoblasts and are no longer mesenchymal stem cells.

With respect to the rejection of claims 1, 4, 6, 9, 11 and 32-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Prockop et al and Matsui et al, Applicant's arguments filed 1/5/2009 have been fully considered but they are not persuasive.

In section 7, the response asserts that one would not combine the teachings of Caplan et al, Prockop and Matsui et al, because one did not have the blueprint of the instant application and the filter membranes of Matsui et al are not the same as the upper plate of the application. This argument is not found persuasive. If the materials are not the same, then the Examiner could not be relying upon the instant application as a blueprint to combine the references. At the same time, Caplan et al teach it is desirable to remove red blood cells from mesenchymal stem cells using a filter. Given the 10 micron pore size of the filter of Prockop et al, one would expect the red blood cells to pass through the filter. Prockop et al teach that smaller mesenchymal stem cells pass through the filter, and, thus, smaller red blood cells would also be able to pass through the filter. Further, the response asserts that Prockop et al teach the separation of RS from non-RS mesenchymal stem cells, but the application separates mesenchymal stem cells from other small-sized cells. This argument is not found persuasive. The combined teachings of Caplan et al, Prockop et al, and Matsui et al will result in the separation of mesenchymal stem cells from small red blood cells. The porous plastic taught by Prockop et al and Matsui et al is a mesenchymal stem cell adhering material. Caplan et al teach that complete medium contains factors that stimulate mesenchymal stem cell growth without differentiation and allows for the selective attachment through specific protein binding sites of only mesenchymal stem cells to

plastic surfaces (e.g., column 9, lines 45-55). Because Caplan et al teach it is within the skill of the art to use a filter to remove red blood cells from mesenchymal stem cells present in bone marrow, and Prockop et al teach the collection of mesenchymal stem cells on a filter of polycarbonate containing 10 micron pores, and Matsui et al teach culturing cells in a device comprising a polycarbonate filter, it would have been obvious to one of ordinary skill in the art to modify the method of Caplan et al to include the addition of cells to a culture device capable of separating mesenchymal stem cells from red blood cells, where the mesenchymal stem cells are cultured on porous plastic, in order to receive the expected benefit of providing an enriched population of mesenchymal stem cells without having to perform the extra steps of using a separate filter and culture device taught by Caplan et al.

The claims encompass the plastic, polycarbonate filter of Prockop et al and Matsui et al. Although Applicant asserts that the materials are not the same as those disclosed in the present specification, the claims are broadly drawn to any mesenchymal stem cell adhering material or any type of plastic. The claims are not limited to the use of materials that are distinguished from the prior art materials.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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